Changes in thrombin generation, fibrinolysis, platelet and endothelial cell activity, and inflammation following endovascular abdominal aortic aneurysm repair

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Background: **Abdominal aortic aneurysm (AAA) is a chronic inflammatory condition associated with a prothrombotic, hypofibrinolytic diathesis that may increase the risk of cardiovascular events. The effect of endovascular aneurysm repair (EVAR) on this prothrombotic diathesis is not fully understood, especially over the medium and long term. A better understanding of these postintervention changes may improve the risk of cardiovascular complications in the long term. The purpose of this study was to examine thrombin generation, fibrinolysis, platelet and endothelial activation, and the inflammatory response during the 12 months following EVAR.**

Methods: **Twenty-nine patients (mean age, 76.9 years) undergoing EVAR for AAA (mean diameter 6.9 cm) had prothrombin fragment (PF) 1 + 2, thrombin-antithrombin complex (TAT), plasminogen activator inhibitor (PAI) activity, tissue plasminogen activator (t-PA) activity and antigen, soluble P- and E-selectin, and highly sensitive C-reactive protein (hsCRP) measured before and at 24 hours, and 1, 6, and 12 months after surgery.**

Results: **PF1 + 2 were markedly elevated prior to EVAR and remained so at 24 hours and 1 month, but had decreased significantly at 6 and 12 months. TAT was also elevated prior to EVAR and increased still further by 24 hours, but fell to below baseline levels thereafter. PAI activity and t-PA antigen were normal prior to EVAR, increased significantly at 24 hours, and then fell to baseline levels. t-PA activity was only detectable at 1 and 6 months; there was a significant rise in soluble P- and E-selectin after EVAR, which was sustained for 12 months. hsCRP increased transiently in response to EVAR but returned to preoperative levels by 1 month.**

Conclusions: **The prothrombotic, hypofibrinolytic diathesis associated with AAA is normalized 12 months after EVAR. This beneficial systemic effect of EVAR for AAA disease may help protect patients against future thromboembolic cardiovascular events. (J Vasc Surg 2012;55:41-6.)**

Abdominal aortic aneurysm (AAA) is associated with deranged hemostasis, endothelial cell (EC) and platelet activation, and cardiovascular morbidity and mortality.[1-14] A recent work from this group has shown that patients with AAA exhibit increased thrombin generation and activity as well as increased fibrin turnover.[15] Although these derangements appear to be correlated with aneurysm size,[14] increased fibrin turnover is also found in patients with small AAA.[1] This may show that hemostatic derangement is related to the size of intrasac thrombus than aneurysm size.[16]

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Both open surgical (OR) and endovascular (EVAR) repair of AAA are associated with increased thrombin generation and relative hypofibrinolysis in the immediate perioperative period.[13,15,17-21] The resultant prothrombotic diathesis after OR and EVAR may account for the high level of peri-operative thrombotic complications.[15] It was found that the hemostatic response is significantly reduced in the long term following OR but not normalized.[22] However, it remains unclear what happens in the long term following EVAR and what the clinical consequences of these hemostatic abnormalities might be for patients. The aim of this study, therefore, was to examine thrombin generation, fibrinolysis, and EC and platelet activation for up to 12 months following elective EVAR.

METHODS

Patients. Ethical approval was obtained. Patients undergoing EVAR and who were willing and able to give fully informed written consent were prospectively recruited. Exclusion criteria were vascular or nonvascular surgical or endovascular procedure within the 3 months prior to EVAR; known inherited or acquired thrombophilia; known disorders of fibrinolysis or platelet function; and anticoagulation therapy with vitamin K antagonists.

Table I. Patients' demographics

Mean age (range)	76.9 years (55.2-88.5)
>75 years (%)	18 (62.1%)
<75 years (%)	11 (3.9%)
Gender (M:F)	27:2 (93.1%: 6.9%)
Hypertension (%)	14 (48.3%)
Ischemic heart disease (%)	16 (55.2%)
Chronic kidney disease (%)	14 (48.3%)
Mean aneurysm size (range)	6.9 cm (5.5-10)
Aneurysm anatomy (%)	
Infra-renal	19 (65.5%)
Endovascular aneurysm repair (%)	
Standard	19 (65.5%)
Fenestrated	10 (34.5%)
Anesthesia	
General	12 (41.4%)
Epidural	17 (58.6%)
Make of stent (%)	
Zenith	23 (79.3%)
Excluder	6 (20.7%)
Patients on antiplatelets (aspirin) (%)	22 (75.9%)

Between July 2008 and April 2009, 35 patients had elective EVAR. Two patients refused to participate in the study, and two were on anticoagulation and were excluded. The remaining 31 patients were recruited. One patient withdrew from the study on the first postoperative day and one died of massive myocardial infarction 3 months after the operation. Twenty-nine patients (27 men and 2 females) of mean age 77 years (range, 55-89 years) and with AAA of mean diameter 6.9 cm (range, 5.5-10 cm) underwent 19 standard and 10 fenestrated EVARs under general (n = 12) or epidural (n = 17) anesthesia. All patients received bolus injection of intravenous heparin (3000 units for standard and 5000 units for fenestrated EVAR) prior to inserting the stent graft. Twenty-two patients were taking aspirin (75 mg daily), 14 were being treated for hypertension, 16 had a history of ischemic heart disease, and 14 had renal impairment (Table I).

Venous blood was collected from the antecubital fossa without tourniquet into sodium citrate tubes before induction of anesthesia and at 1 day and 1, 6, and 12 months postoperatively. Samples were centrifuged for 15 minutes at 3500 revolutions per minute within 30 minutes of collection; plasma was isolated, aliquoted, and stored at −80°C for later batch analysis.

Markers of thrombin generation and neutralization. Prothrombin fragment (PF) 1 + 2 (USCN Life Science Inc, Wuhan, China) and thrombin-antithrombin complexes (TAT; Enzygnost TAT Micro, Siemens Healthcare Diagnostics Inc, Deerfield, Ill) were measured (Fig 1).

Markers of fibrinolysis. Plasminogen activator inhibitor (PAI) activity (Technozym PAI-1 Actibind; Technoclone Ltd, Surrey, United Kingdom) and tissue plasminogen activator (t-PA) antigen and activity (t-PA Combi Actibind; Technoclone Ltd) were measured (Fig 2).

Markers of platelet and endothelial activation and inflammation. Soluble (s)P-selectin was measured as a marker of platelet activation, sE-selectin as a marker of EC activation[23,24] (IBL International GMBH, Hamburg, Germany), and highly sensitive C-reactive protein (hs-CRP) was measured as a marker of the inflammatory response.

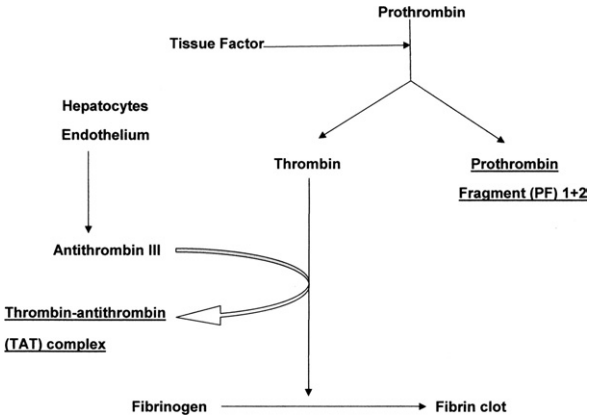

Fig 1. Mechanism of the coagulation system. Tissue injury, endothelial activation and injury, and monocyte activation lead to tissue factor release. This triggers the extrinsic coagulation cascade. This results in conversion of prothrombin into thrombin and prothrombin fragment (*PF*) 1 + 2. Thrombin is inactivated by antithrombin III, leading to formation of thrombin-antithrombin complex (*TAT*).

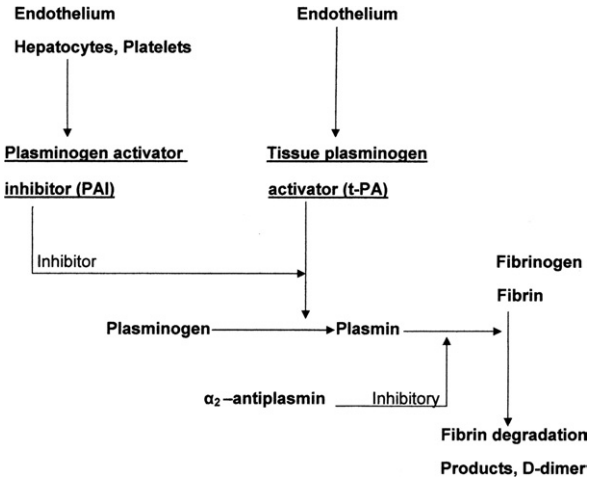

Fig 2. Mechanism of the fibrinolytic system. Endothelial activation and injury causes the release of tissue plasminogen activator (*t-PA*) antigen, which converts plasminogen into the active plasmin. This active enzyme leads to the breakdown of fibrinogen, fibrin, and fibrin clot to fibrin degradation products. Plasminogen activator inhibitor (*PAI*) is released from the endothelium, hepatocytes, and platelets to inhibit t-PA.

Tests were performed using the fully automated, multibatch and multi-test Triturus EIA Analyzer (Grifols USA, LLC, Los Angeles, Calif) according to the manufacturer's instructions.

Statistical analysis. The groups were compared using the Friedman test. Changes in variables over time were analyzed using Dunn's multiple comparison test

Table II. Changes in different markers over time (median and IQR)

	Preoperative median (IQR)	*24 Hours median (IQR)*	*1 Month median (IQR)*	*6 Months median (IQR)*	*12 Months median (IQR)*
Prothrombin fragment 1 + 2 (0.4-1.1 nmol/L)	2.1 (1.5-3.7)	2 (1.4-2.9)	2.1 (1.6-3.4)	1.9 (1.2-2.5)[a]	1 (0.7-2)[a]
Thrombin-antithrombin complex (1-4.1 μg/L)	6.2 (4.4-15.6)	14 (11-24.6)[a]	8.1 (5.4-14.3)	8.9 (5.1-11.6)	7 (5.1-11)
Plasminogen activator inhibitor activity (1-7 U/mL)	4.9 (0.3-6.8)	8.5 (0.3-10.6)[a]	0.3 (0.3-3)[a]	0.3 (0.3-4)[a]	5.7 (3.8-7.7)
Tissue plasminogen activator antigen (2-8 ng/mL)	3.4 (2.6-4.4)	5.1 (3.1-6.4)[a]	3.5 (2.4-5.4)	1.2 (1-2.2)[a]	3.4 (2.4-4.5)
Tissue plasminogen activator activity (0 U/mL) mean (±SD)	0 (0)	0 (0)	0.046 (0.09)[a]	0.023 (0.06)[a]	0 (0)
sP-selectin (92-212 ng/mL)	71 (61-86)	80 (61-93)	113 (80-141.5)[a]	110 (73.5-139.5)[a]	87 (61-116)[a]
E-selectin (17.5-88.1 ng/mL)	14 (9-18)	24.5 (12.5-42.5)[a]	15 (9-22)	52 (23.5-59.5)[a]	38 (24-42)[a]
Highly sensitive C-reactive protein (mg/L)	4.3 (1.5-12.75)	82.2 (53-105.5)[a]	7 (3.3-19)	4.3 (2.1-16.3)	2.7 (1.2-11.6)

IQR, Interquartile range; *SD*, standard deviation.
[a]$P < .05$ against preoperative values.

and Wilcoxon signed rank paired test. Because data were not normally distributed, they were log transformed to determine the effects of covariables on the results using the parametric independent-sample *t* test.

Calculations were performed using SPSS for Windows (version 16.0; SPSS Inc, Chicago, Ill) and GraphPad Prism 5 for Windows (version 5.03; GraphPad Software Inc, La Jolla, Calif). A *P* value of less than 0.05 was considered statistically significant. Unless specified otherwise, median and interquartile ranges (IQR) were used.

RESULTS

Patients and stent grafts

All stent grafts (23 Zenith; Cook Inc, Bloomington, Ind and 6 Excluder; W. L. Gore Inc, Flagstaff, Ariz) were implanted successfully. No patient required peri-operative blood transfusion.

Three patients required reintervention at 6 months for claudication; two underwent angioplasty and a third had common femoral artery endarterectomy and angioplasty. Two other patients developed asymptomatic type II endoleaks, which were treated conservatively. Changes in hemostatic, endothelial, platelet, and inflammatory markers are summarized in Table II.

Markers of coagulation

PF 1 + 2 did not change significantly from baseline to either 24 hours or 1 month, but there was a significant fall by 6 and 12 months (Fig 3, *A*).

TAT increased significantly at 24 hours postoperatively, followed by return to the preoperative levels at 1, 6, and 12 months postoperatively (Fig 3, *B*).

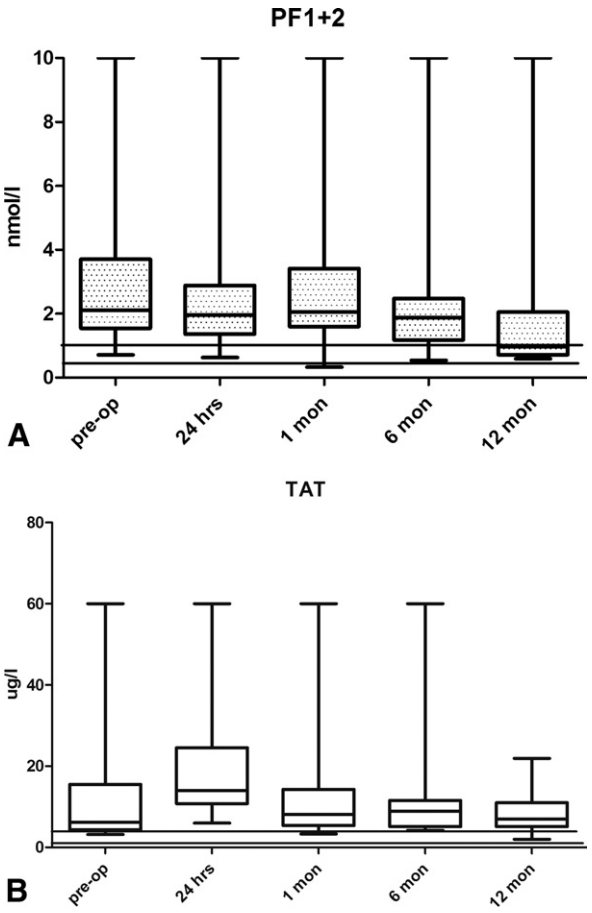

Fig 3. (A) Changes in prothrombin fragment (*PF*) 1+2. **(B)** Changes in thrombin-antithrombin complex (*TAT*). Horizontal lines represent the normal range (manufacturer's range). *Error bars* represent the minimum and maximum and the rectangles represent the median and interquartile range (IQR).

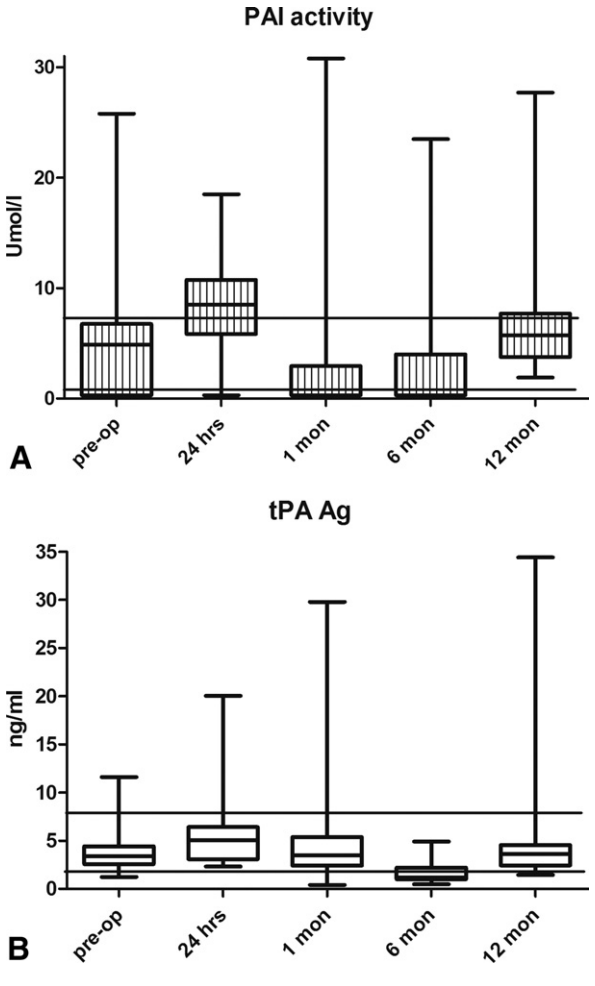

Fig 4. (A) Changes in plasminogen activator inhibitor (*PAI*) activity. **(B)** Changes in tissue plasminogen activator (*t-PA*) antigen.

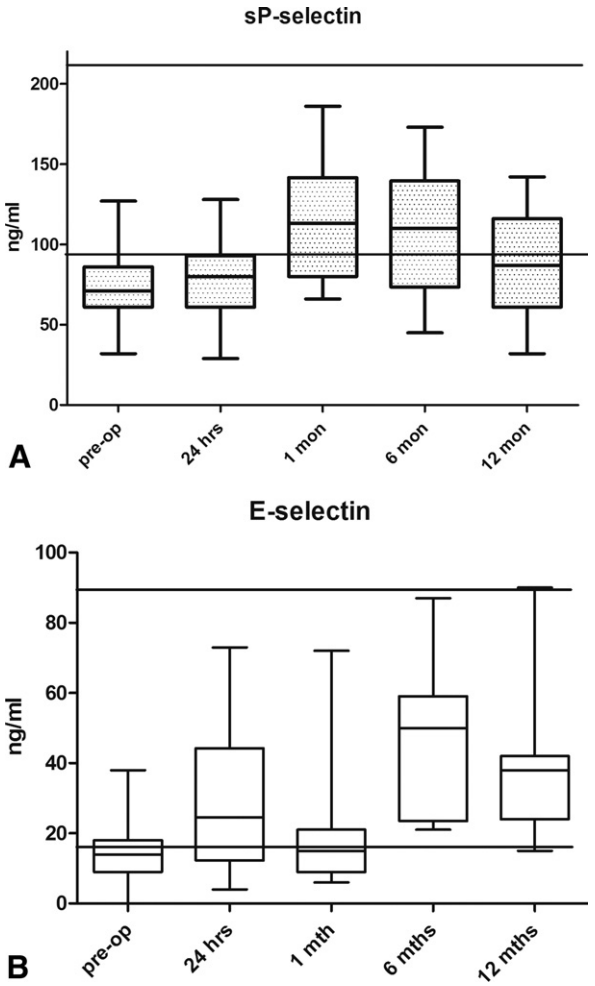

Fig 5. (A) Changes in sP-selectin. **(B)** Changes in sE-selectin.

Markers of fibrinolysis

PAI activity increased significantly at 24 hours, followed by a significant drop at 1 and 6 months. At 12 months, there was a significant increase in PAI, leading to a return to the preoperative levels (Fig 4, *A*).

t-PA antigen increased significantly at 24 hours and then returned to the baseline level at 1 month. This was followed by a significant reduction at 6 months and a return to preoperative values at 12 months (Fig 4, *B*).

t-PA activity was unchanged at 24 hours, followed by a significant increase at 1 and 6 months and a return to preoperative level at 12 months.

Platelet activation. sP-selectin did not change at 24 hours, but at 1 month there was a significant elevation that was sustained at 6 months. There was a significant drop at 12 months, but the median value was significantly higher than preoperatively. Patients with ischemic heart disease and those who were on antiplatelet treatment before the operation had significantly lower sP-selectin levels.

Endothelial activation. sE-selectin increased significantly at 24 hours, followed by return to preoperative value at 1 month and a significant increase at six and 12 months (Fig 5).

Inflammatory response. hsCRP increased significantly at 24 hours and then returned to baseline level at 1 month and did not change significantly at 6 or 12 months. Patients with infra-renal AAA had significantly lower preoperative hsCRP ($P < .003$). When the inflammatory response to EVAR was compared between patients, those who had fenestrated EVAR had a significantly higher response at 1 ($P = .012$), 6 ($P = .009$), and 12 ($P = .021$) months than patients who had standard EVAR.

Correlation of different markers, aneurysm size and demographics. Aneurysm size did not correlate with coagulation, fibrinolytic, or inflammatory markers pre- or postoperatively. TAT and PF1 + 2 did not correlate at any time point. PAI activity correlated significantly with t-PA antigen at all time points ($P < .001$). sP-selectin and E-selectin did not correlate at any time point.

DISCUSSION

Previous case reports have described disseminated intravascular coagulopathy (DIC) following EVAR.[25,26] It has been suggested that continued perfusion of a thrombus-filled aneurysm sac might predispose to an acute-on-chronic consumptive coagulopathy.[27,28]

The present study confirms that patients with asymptomatic AAA exhibit a prothrombotic diathesis characterized by excessive thrombin generation as shown by markedly elevated PF1 + 2 and TAT prior to EVAR.[4,15,17,19-22] However, unlike some previous studies, no correlation was found between TAT, PF1 + 2, and aneurysm diameter in this cohort.

The different behavior of PF1 + 2 and TAT in response to EVAR and the lack of correlation between these two markers before and after the operation suggest they represent different responses (Fig 3). High levels of PF1 + 2 and TAT indicate excess thrombin production and neutralization, respectively. PF1 + 2 remained unchanged from baseline at 24 hours and 1 month postoperatively, indicating no increase in thrombin generation in response to EVAR. At 6 months, it decreased significantly; however, it was still higher than the normal range. At 12 months, PF1 + 2 dropped significantly below the preoperative level to reach normal values, suggesting normalization of thrombin generation at 1 year post-EVAR. This indicates that the presence of the thrombus in the isolated aneurysm sac does not induce thrombin production as previously suggested.[20,29]

The significant increase in TAT at 24 hours postoperatively may be explained by increased binding with antithrombin III in response to manipulation during insertion of the stent graft. Shimazaki et al[18] and Monaco et al[21] showed a significant reduction in antithrombin III and a significant increase in TAT on the first postoperative day. They showed return of antithrombin III to baseline on the first week after the operation, which then remained unchanged. Results similar to ours were observed at short-term in previous studies.[17,18,20]

This is the first report to describe normalization of thrombin generation detected 1 year following EVAR. The combination of no increase in thrombin generation and increased thrombin neutralization following EVAR may be protective against cardiovascular complications and thromboembolic disorders in this group of patients.

Similar to previous studies, we found preoperative PAI activity and t-PA antigen and activity to be within the normal range.[14,17,19] While one might conclude that this indicates normal fibrinolysis, given the very high levels of thrombin generation, one might expect fibrinolysis to be activated with elevated t-PA activity and reduced PAI activity. That this appears not to be the case suggests that, in fact, these AAA patients have relative hypofibrinolysis that might further predispose them to thrombotic problems. Indeed, PAI activity increased significantly to above the normal range on the first postoperative day, following which levels dropped below baseline levels (although most values were still in the normal range). Aho et al[17] described a significant increase in PAI activity at day 1 postoperatively, temporary decrease at day 3, increase again at day 7, and return to preoperative levels at 3 months. The postoperative fibrinolytic response showed low fibrinolytic activity on the first postoperative day, which may be due to the surgical trauma, high fibrinolytic activity at 1 and 6 months, and return to normal fibrinolytic activity 12 months following EVAR. The expected correlation between PAI activity and t-PA antigen at all time points indicates the validity of the analysis (Fig 4).

The significant increase in platelet activity, as represented by elevated sP-selectin during the first postoperative year, may justify giving dual antiplatelet therapy to patients following EVAR, especially during the first year after the operation. Aho et al described a significant reduction in sP-selectin on the third postoperative day, with increase above the baseline 3 months following EVAR.[17] The significant increase in sE-selectin that was observed on the first postoperative day could be due to the manipulation during insertion of the stent graft. The absence of correlation between sP- and sE-selectin at all time points and their different responses to EVAR may indicate that they did not arise from the same source (Fig 5).

The increase in hsCRP demonstrated on day 1 occurred in response to the surgical trauma. However, there was no significant difference in the inflammatory response, from the baseline level, at 1, 6, and 12 months postoperatively. Previous studies have detected the maximum increase in CRP on the second and third days following EVAR.[17,20] The significantly lower hsCRP in patients with infra-renal AAA preoperatively and the higher response in patients who had fenestrated EVAR postoperatively may indicate that the inflammatory response is related to the extent of the aneurysm rather than the size. A correlation between CRP and the volume of the intramural thrombus has been previously described.[17]

In conclusion, this report shows, for the first time, that the prothrombotic, hypo-fibrinolytic diathesis associated with AAA is normalized 12 months after EVAR. This beneficial systemic effect of EVAR for AAA disease may help protect patients against future thromboembolic cardiovascular events.

AUTHOR CONTRIBUTIONS

Conception and design: MA, DA, RV, AB
Analysis and interpretation: MA, RD
Data collection: MA, RD
Writing the article: MA
Critical revision of the article: MA, DA, RV, AB
Final approval of the article: MA, RD, DA, RV, AB
Statistical analysis: MA
Obtained funding: DA
Overall responsibility: MA

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